SYNTHESIS
STEREOCHEMISTRY AND DYNAMIC BEHAVIOUR
OF
SOME THIOACRYLAMIDES

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by
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ABBREVIATIONS

DMF	Dimethylformamide
dPM	Dipivalo-methanato
Fig	Figure
E	Electrophilic
fod	Heptafluoro-dimethyloctanedienato
IR	Infrared
LIS	Lanthanide induced shift
LSR	Lanthanide shift reagent
Me	Methyl
M.P.	Melting point
NMR	Nuclear magnetic resonance
Nu	Nucleophilic
Ph	Phenyl
tmhd	Tetramethyl heptane dienato

Abstract

SYNTHESIS

Stereochemistry and Dynamic Behavior of Some Thioacrylamides

by

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The reaction of N,N-Dimethylamides with the dimer of p-methoxyphenylthionophosphine sulfide (Lawesson's reagent) gives N,N-Dimethylthioamides. By treating these disubstituted thioamides with (i) the Vilsmeir - Haack Arnold complex (formamide chloride) and (ii) Bis-(dimethylamino)-tert-butoxy methane, model compounds ($Me_2N-CH=C(R)-\overset{S}{\overset{\|}{C}}-NR_2$) were synthesized. Substitution reactions were also carried out using these model compounds (3-aminothioacrylamides) or their iminium salts with a primary amine (p-anisidine) to synthesize the corresponding 3-anisidinothioacrylamides. The reactions were successful and yields were nearly quantitative.

The dynamic behaviour and the ground state stereochemistry of these model compounds have been studied. Based on ^1H-NMR study and LIS investigation, rotational barriers as well as the preferred conformation of some of these model compounds have been determined from the proposed three dimensional geometries.

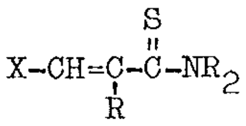
Introduction

Heterocyclic compounds are very widely distributed in nature, and are essential to life in various ways.[1] Many drugs, dyes, pesticides, metabolically important substances etc are heterocyclic compounds.

One of the fundamental requirements in the synthesis of heterocyclic compounds with one or more heteroatoms is the availability of suitably functionalized starting materials. During the past few years, many synthetic routes which serve as suitable reactive intermediates for the synthesis of heterocyclic compounds have been developed. The most important methodologies in this catagory include

a. Addition of amines to isothiocyanates.[2]
b. Reaction of amines with 3-amino dithioacrylic esters.[3]
c. Addition of hydrogen sulfide to 3-aminoacrylonitriles.[4]
d. Reaction of (substituted) thioacetamide with dimethyl formamide dimethyl acetal[5] or Bis-(dimethylamino)-tert-(butoxy) methane.[6]
e. Ring cleavage of trithiones with amines.[7]
f. Addition of thioacetic acid to 3-amino propynal.[8]

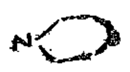
Recently Liebscher et al[9] found a new route to a series of 3-amino and 3-hydroxy thioacrylamides (1 and 2).



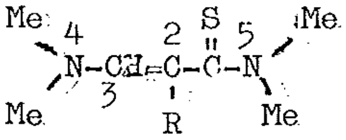
$$X{-}CH{=}\underset{R}{C}{-}\overset{S}{\overset{\parallel}{C}}{-}NR_2$$

1. $X = NR_2$
2. $X = OH$

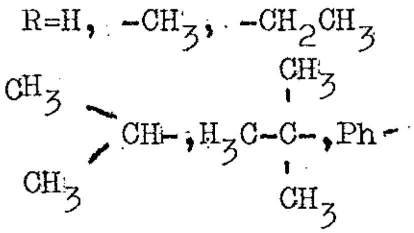
R =



These compounds are very reactive towards cyclization and substitution reactions. A number of thiophene, pyrazole etc derivatives were synthesized by Liebscher et al[10] starting from 1 and 2. This new finding being the starting point, our main interest in this research is to synthesize similar reactive intermediates 3 with different alkyl and aryl groups for dynamic NMR and stereochemical studies. To our knowledge, prior to our work, there has been no report in the literature of any attempt to study the dynamic behaviour as well as the ground state stereochemistry of these compounds.

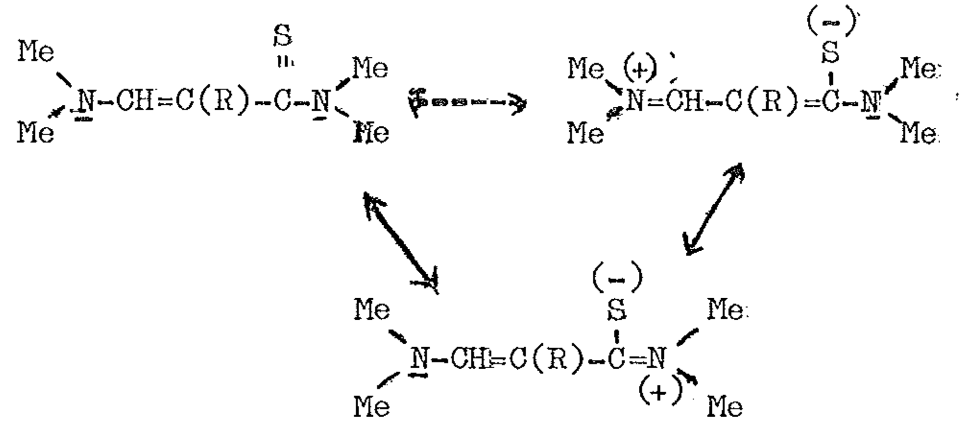


3



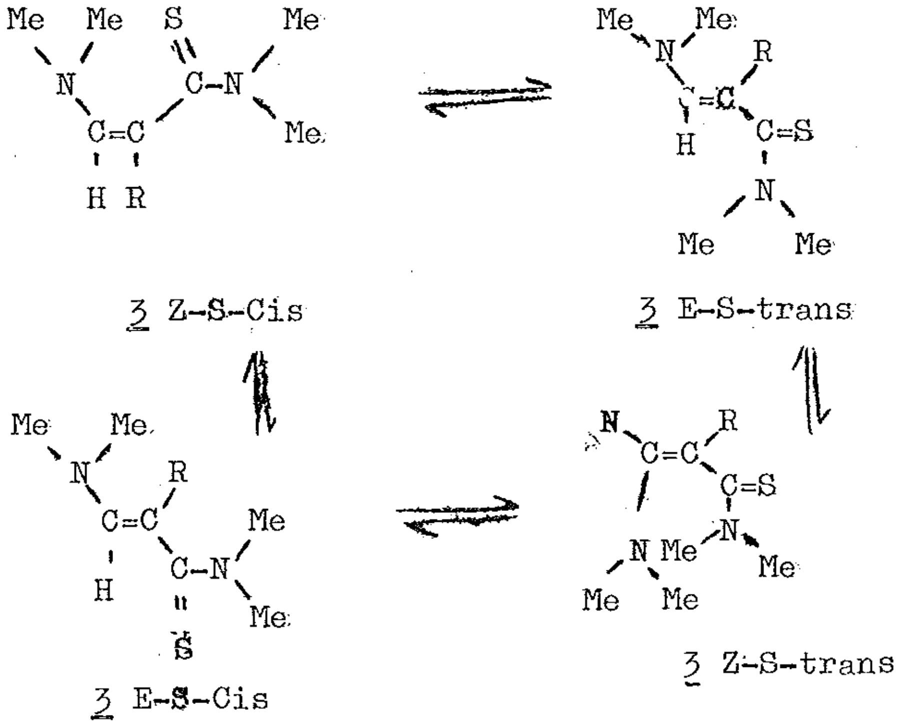
R=H, $-CH_3$, $-CH_2CH_3$, $(CH_3)_2CH-$, $H_3C-C(CH_3)_2-$, $Ph-$

The main advantage of these compounds 3 over the morpholino analoges 1 and 2 is their spectroscopic properties. Due to the complicated methylene proton peak, the morpholino analoges 1 and 2 are not very useful for dynamic nmr and lathanide induced shift (LIS) investigation. The relatively simple dimethylamino nmr signals in 3 together with the expected push pull effect (scheme 1) make these reactive intermediates specially suitable for such studies.



Scheme (1)

In connection with the dynamic behaviour, the ground state stereochemistry of these compounds is the other interesting aspect to look into i.e. determining the con formation of



Scheme 2

such compounds from the proposed three dimensional geometries (scheme 2) will help one in understanding the conformation of related systems beyond reflecting the validity of the LIS method for stereochemical studies.

2. Synthesis

2.1 Amides

Various methods are known for preparing N,N-Dimethylamides, some of these methods include.[11,12,13]

1. The reaction of acid halides with dimethylamine[11] (eq. 1).

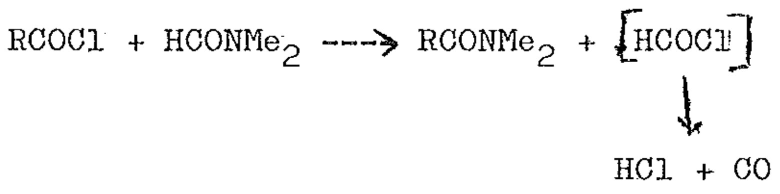
$$RCOCl + HNMe_2 \dashrightarrow RCONMe_2 + HCl \qquad (eq.\ 1)$$

2. The reaction of carboxylic acids with dimethyl amine (eq. 2).

$$RCOOH + HNMe_2 \rightleftharpoons RCOONMe_2 + H_2O \qquad (eq.\ 2)$$

Eq. 2 is reversible. Therefore one needs to remove the water continiously from the reaction mixture.

The disubstituted amides needed in this research are easily synthesized from the corresponding acid halides or anhydrides and N,N-Dimethyl formamide[13] (scheme 3).



$$\mathrm{RCOCl} + \mathrm{HCONMe_2} \dashrightarrow \mathrm{RCONMe_2} + \underset{\substack{\downarrow \\ \mathrm{HCl} + \mathrm{CO}}}{[\mathrm{HCOCl}]}$$

Scheme 3

The advantage of this method over the customary preparative methods (eq. 1 and 2) is that, it avoids the somewhat objectionable dimethylamine by substituting N,N-Dimethyl-formamide for it. The method also has the added advantage of easy workup as no solvent is used. Table 1 lists the various amides synthesized following this synthetic method. The procedures for the preparation of compounds 4 and 7 are given in the experimental section. (See section 5). Compounds 5 and 6 were prepared in the same way as compound 7.

Table 1. Data table for N,N-Dimethylamides

Compound	Structure
4	$CH_3CH_2CONMe_2$
5	$CH_3CH_2CH_2CONMe_2$
6	$Me_2CHCH_2CONMe_2$
7	$PhCH_2CONMe_2$

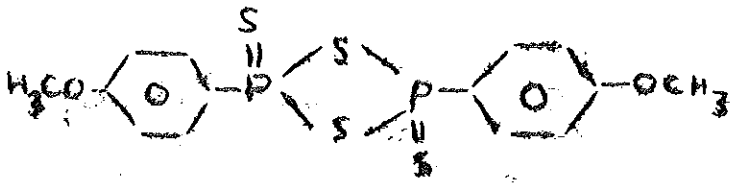
2.2 Thioamides

The most common procedures for the preparation of thioamides are

1. The reaction of amides with phosphorus pentasulfide.[14]
2. The Willgerodt - Kindler reaction.[15]

   In this method aldehydes or ketones are heated with equimolar amounts of sulfur and an amine under anhydrous conditions. Thioamides are isolated as the principal products.
3. The reaction of aldehydes or ketones with dimethylammonium chloride, sulfur and anahydrous sodium acetate.[16] (A modification of Willgerodt-reaction.)
4. The reaction of acylchlorides with hydrogen sulfide.[17]
5. The reaction of amides with the Lawesson's reagent.[18]

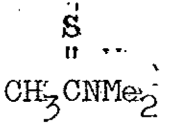
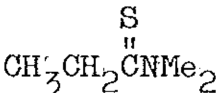
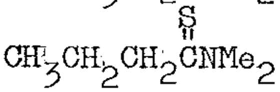
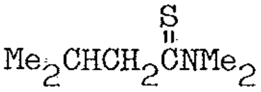
   The dimer of p-methoxy thionophosphine 8 (Lawesson's reagent) is known for the thiation of ketones, carboxamides, esters, lactones, imides, enamines and S-substituted thioesters.[19-22]

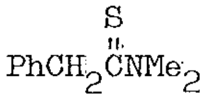
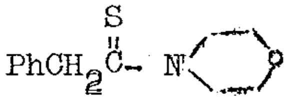


8

The reaction of amides with 8 is claimed to be superior to all others as in most cases quantitative yields are found. The only problem is product isolation which is quite tedious. All the thioamides required for this study were synthesized by this method. Unlike the reported cases, yields were however very low. The synthesized thioamides are tabulated below. Table 2. Compound 8 was prepared from anisole and P_2S_5[20].

Table 2. Data table for N,N-Dimethylthioamides

Compound	Structure
9	 $CH_3\overset{\overset{S}{\|}}{C}NMe_2$
10	 $CH_3CH_2\overset{\overset{S}{\|}}{C}NMe_2$
11	 $CH_3CH_2CH_2\overset{\overset{S}{\|}}{C}NMe_2$
12	 $Me_2CHCH_2\overset{\overset{S}{\|}}{C}NMe_2$

Compound	Structure
13	 $PhCH_2\overset{\overset{S}{\|}}{C}NMe_2$
14	

2.3 Thioacrylamides

It has been known that the reaction of an active methylene compound with a Vilsmeier complex, the adduct of N,N-Dimethylormamide (DMF) with phosphorus-oxychloride or phosgen, affords N,N-Dimethylamino derivatives.

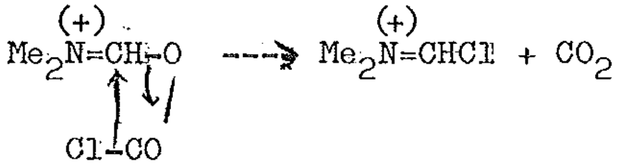
The Vilsmeier reagent is a cationic species regarded by Arnold,[23] as having the structure

$$R_2\overset{(+)}{N} = CHX \longleftrightarrow R_2\overset{-}{N} - \overset{(+)}{C}HX$$

15 16

where X is a halogen (Cl or Br) atom or other electronegative groups such as $-O.PO.Cl_2$. It is prepared by treating a formamide, generally DMF, with phosgen or phosphoryl chloride, and the reactions are believed to proceed as follows eq. 3 and 4.

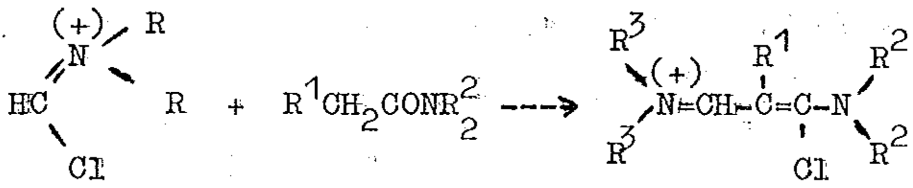
a. $Me_2N\text{-}CH{=}O + COCl_2 \dashrightarrow Me_2\overset{(+)}{N}{=}CH\text{-}O.COCl + Cl^-$ (eq. 3)



$$Me_2\overset{(+)}{N}{=}CH\text{-}O \dashrightarrow Me_2\overset{(+)}{N}{=}CHCl + CO_2$$ (eq. 4)

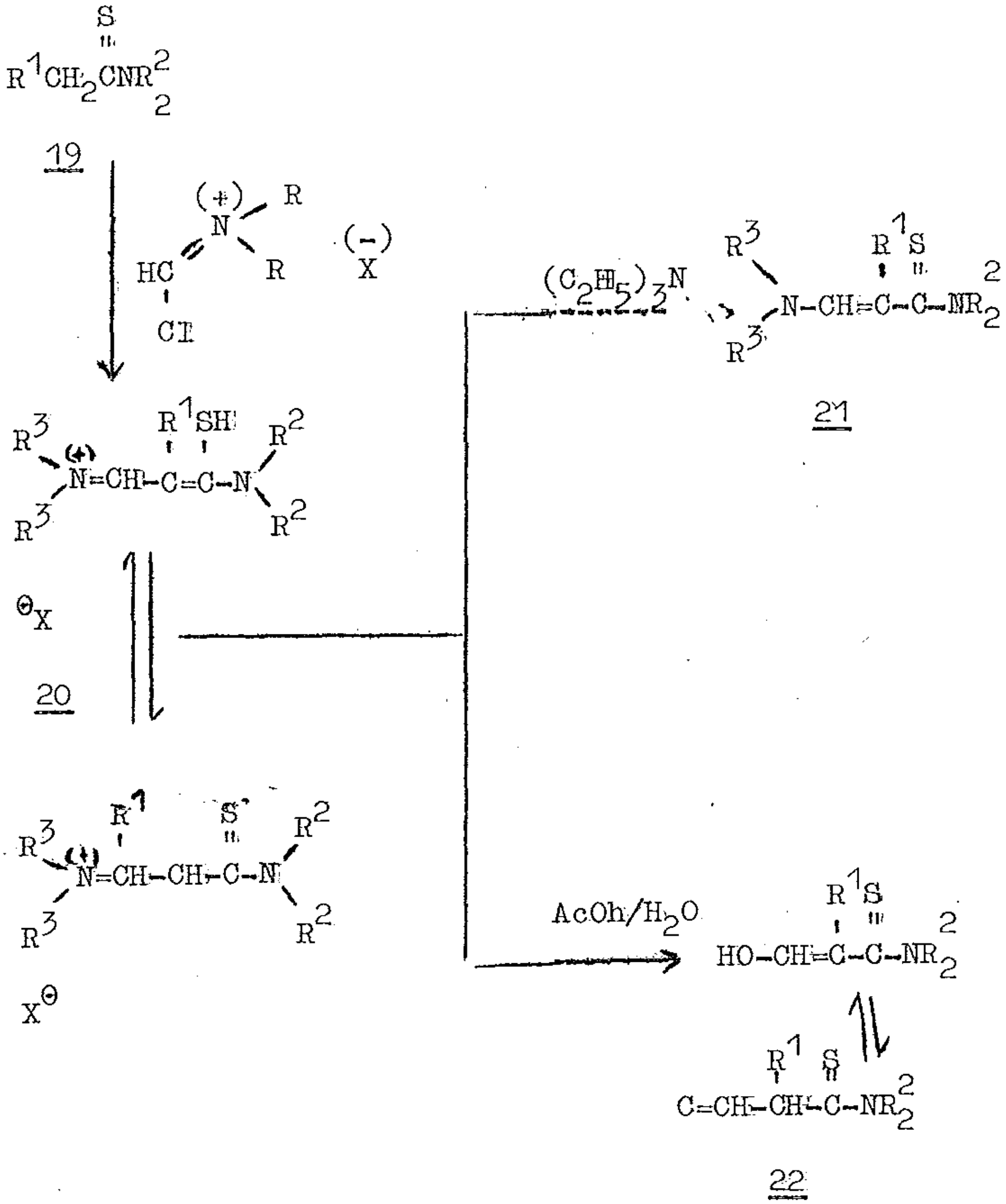
b. $Me_2N\text{-}CHO + POCl_3 \dashrightarrow Me_2\overset{(+)}{N}{=}CH\text{-}O\text{-}POCl_2 + Cl^-$ (eq. 5)

The application of 15 in imino formylation reactions has been studied by Arnold et al.[24,23] The reaction of this intermediate (15)with alkane amides[24,25] has also been studied and results in chlorination iminomethylation with substitution of the carbonyl O-atom by chlorine to give products of type 18.



15 17 18

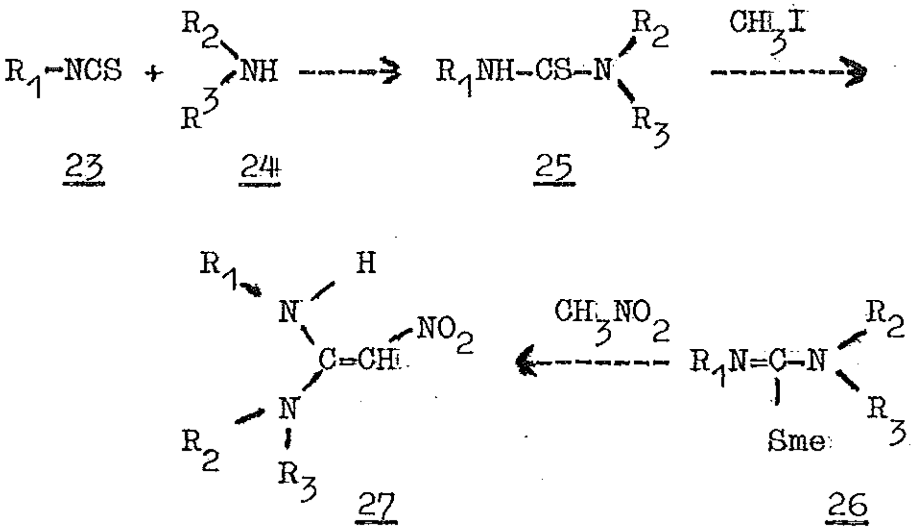
Liebscher et al[10] also synthesized a number of 3-amino and 3-hydroxy-thioacrylamides by treating substituted thioacetamides with formamide chlorides. Scheme 4.



Scheme 4

Compounds related to 21 and 22 have also been synthesized by a number of other methods.[2,3,5,6,7] These methods include

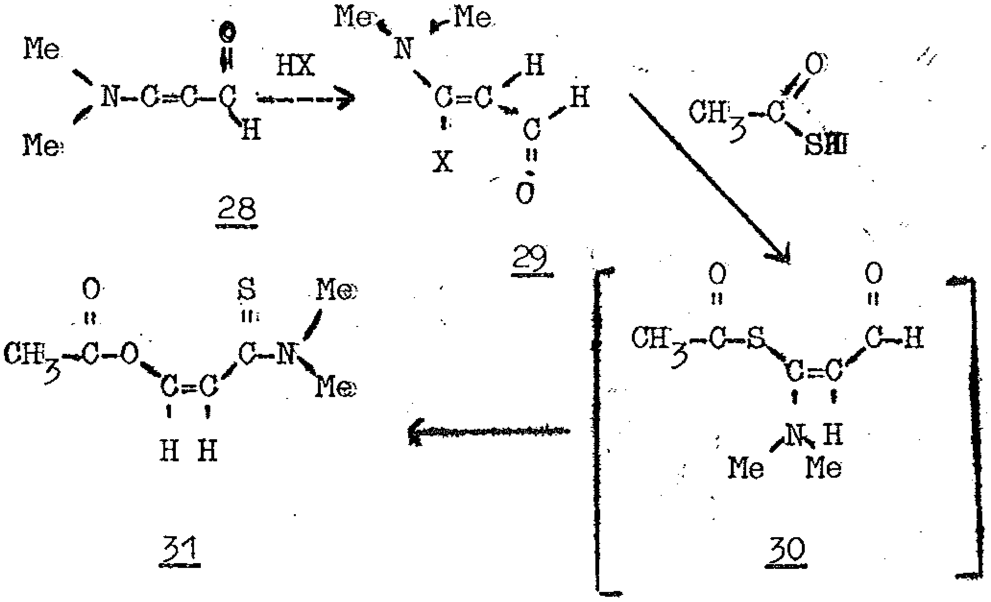
a. Addition of amines to isothiocyanates.[2] Scheme 5.



Scheme 5

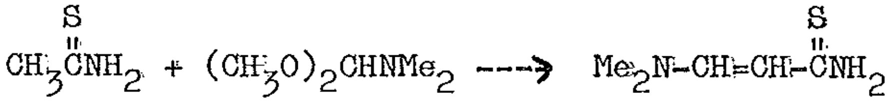
b. Addition of thioacetic acid to 3-amino propynal.

Scheme 6



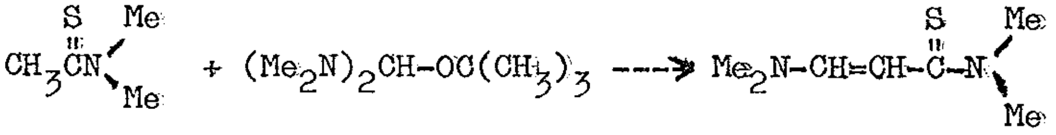
Scheme 6

c. Reaction of (substituted) thioacetamides with dimethylformamide dimethylacetal (<u>33</u>)^5 and Bis-(dimethylamino)-tert. butoxymethane (<u>36</u>)^6.



$$CH_3\overset{S}{\overset{\|}{C}}NH_2 + (CH_3O)_2CHNMe_2 \dashrightarrow Me_2N{-}CH{=}CH{-}\overset{S}{\overset{\|}{C}}NH_2$$

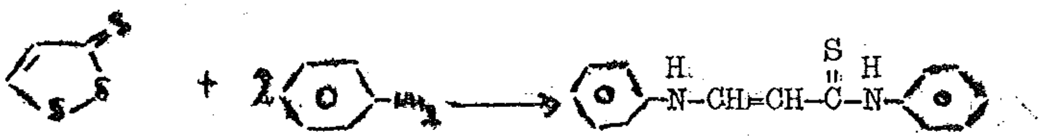
<u>32</u> <u>33</u> <u>34</u>



$$CH_3\overset{S}{\overset{\|}{C}}N\begin{array}{l}Me\\Me\end{array} + (Me_2N)_2CH{-}OC(CH_3)_3 \dashrightarrow Me_2N{-}CH{=}CH{-}\overset{S}{\overset{\|}{C}}{-}N\begin{array}{l}Me\\Me\end{array}$$

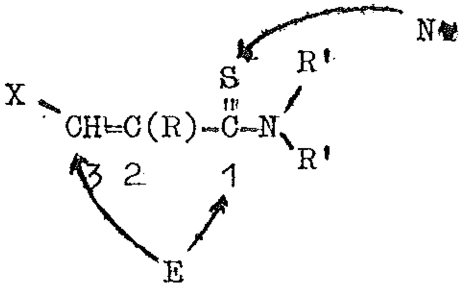
<u>35</u> <u>36</u> <u>37</u>

d. Ring cleavage of trithiones (<u>38</u>) with amine (<u>39</u>) also results in a rearranged product with loss of sulphur to give derivatives of 3-amino thioacrylamides^7(40).

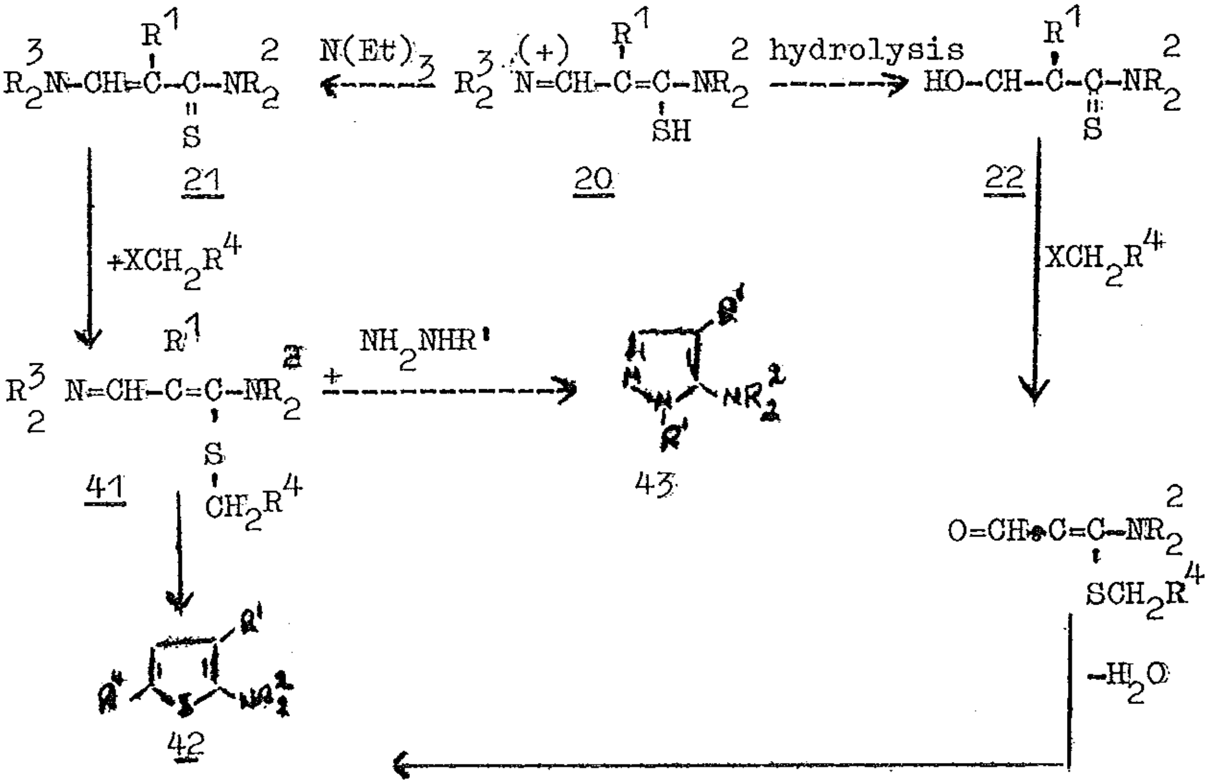


<u>38</u> <u>39</u> <u>40</u>

structurally thioacrylamides can be considered as polyfunctional systems possessing nucleophilic properties at the thiocarbonyl sulfur and electrophilic carbon atoms in position, 1 and 3.



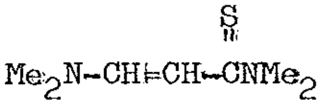
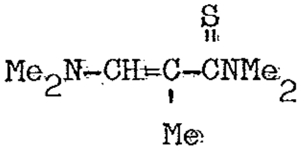
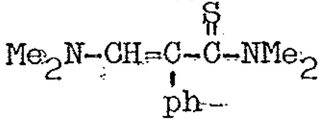
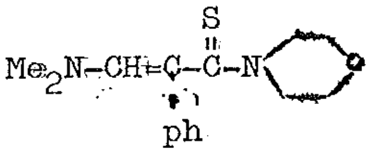
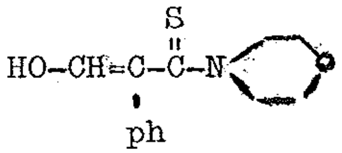
This polyfunctionality is responsible for their reactivity and applicability in the synthesis of many hetrocyclic compounds. By making use of these properties, Liebscher et al[10] synthesized a number of thiophene, pyrazole etc derivatives by treating 3-amino- and 3-hydroxy-thiocrylamides with alkalating agents such as dimethylsulfate, subsitituted methylhalides like bromonitromethane and binucleophiles such as hydrazine. Scheme: 7.

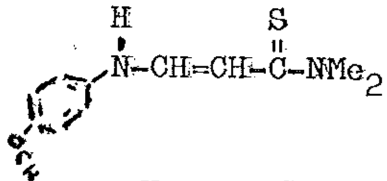
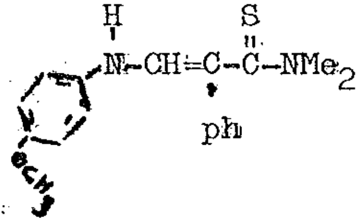


Scheme 7

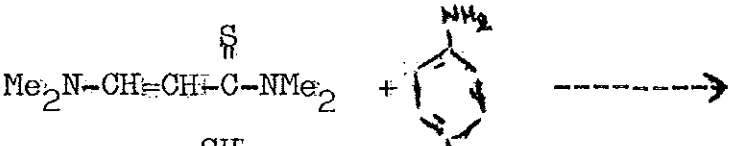
As mentioned in the introductory part, our main interest in this research is to synthesize compounds 3 and to study their dynamic behaviour as well as their ground state stereochemistry. Various methods were applied to synthesize some of the wanted thiocrylamides. The synthesized thioacrylamides are tabulated below. Table 3.

Table 3. Data table for thioacrylamides

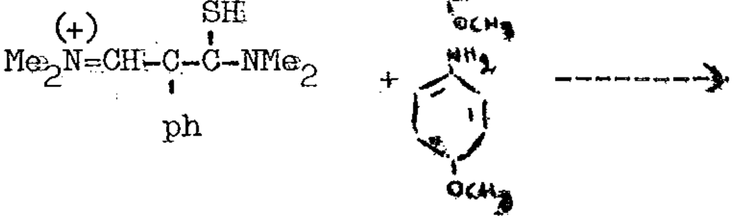
Compound	Structure
47	 $Me_2N-CH=CH-\overset{\overset{S}{\|}}{C}NMe_2$
48	 $Me_2N-CH=\underset{\underset{Me}{\mid}}{C}-\overset{\overset{S}{\|}}{C}NMe_2$
49	 $Me_2N-CH=\underset{\underset{ph}{\mid}}{C}-\overset{\overset{S}{\|}}{C}-NMe_2$
50	
51	

Compound	Structure
52	
53	

Compounds 49, 50 and 51 were synthesized by making use of the general procedure of Liebscher et al.[9] 47 and 48 by reaction of the corresponding thioamides with Bis-(dimethylamino)-tert-butoxymethane[6] and compounds 52 and 53 are the results of substitution reactions (eq. 6 and 7).



52 (eq. 6)



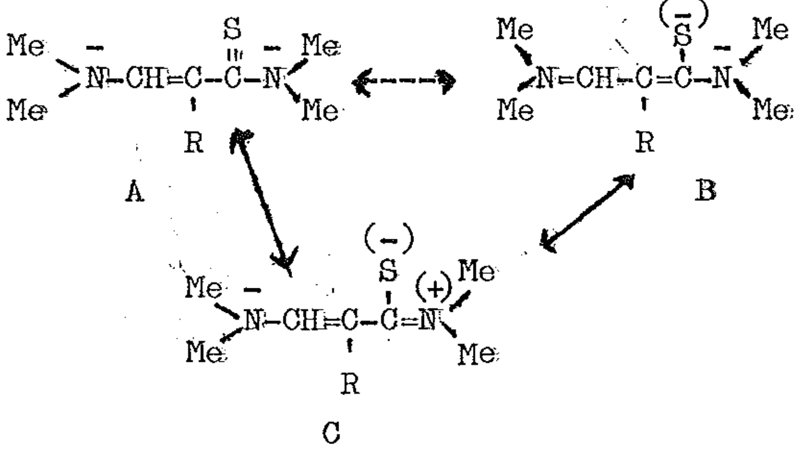
53 (eq. 7)

3. Stereochemical studies

3.1 Dynamic NMR spectroscopy

Free rotation about a bond in a molecule may be sterically and electronically hindered. Very many cases consistent with these factors are known. One can mention the stability of cis-trans isomers about the C,C-double bond (very stable conformational isomers) and restricted rotation about a C,C-single bond (well known example of atropisomerism in biphenyl derivatives). Free rotation about a C,C-single bond can also be restricted by mesomeric interactions, a factor which gives single bonds some double bond character.

Consideration of the structure of thioacrylamides 3 suggests, to that these compounds are representatives of push pull olefins. Due to possible cannonical forms (B and C), these compounds are expected to show restricted rotation about the different C,N-and C,C-partial double bonds.



Such rotational barriers can be inferred from the temperature dependence of the compounds NMR spectra.

NMR spectroscopy has been widely applied for determining rotational barriers of this kind since the discovery of the hinderance of rotation in dimethylformamide by Phillips,[26] the first application of NMR method to the study of kinetic processes.

Considering the NMR spectra of 3 at room temperature, the two methyl groups on N-5 and N-4 are chemically identical but magnetically non-equivalent i.e. in the NMR spectrum, the two groups are not equivalent due to anisotropy of the diamagnetic susceptibility of the thiocarbonyl group, but rotation about the carbon-nitrogen bond leads to "exchange" of the two methyl groups. Under conditions of slow isomerization, this process leads to two separate signals for the two methyl groups in the NMR spectrum, while "fast" rotation gives only one signal with an intermediate chemical shifts. (Fig 1).

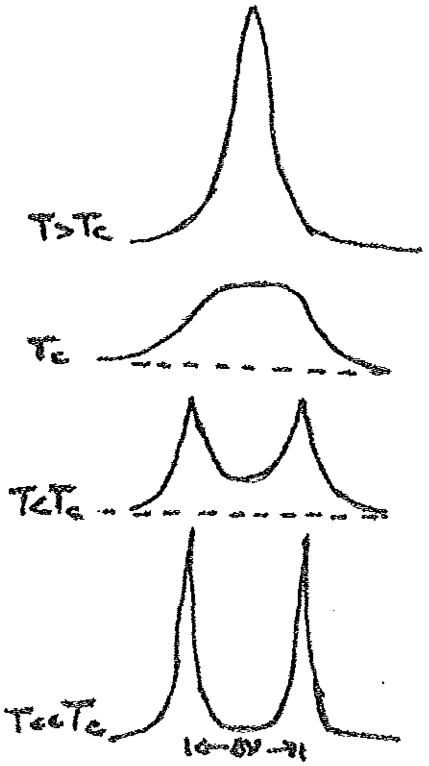


Fig. 1. Temperature dependence of NMR spectrum as a result of chemical exchange (uncoupled AB case.)-T_c = coalescence temperature).

For thermally induced rotations, the NMR spectra are particularly temperature dependent in the transition region between "slow" and "fast" rotation (Fig. 1) and can be used to determine rate constants. The activation parameters ($\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, ΔS^{+},ΔEa) can then be determined from the rate constant (k_r) by classical chemical kinetics, using the shape of the signal in the transition region. To determine k_r, several methods of evaluation are available in practice:

1. by approximation equations[27]
2. by graphical evaluation of certain spectral parameters[28]
3. by computer matching of measured and calculated spectra[29]

A particularly simple situation occurs when two atoms or groups of atoms with initially sharp signals of equal intensity undergo chemical exchange (uncoupled AB case). (Fig. 1). For evaluation by approximation equations, dynamic NMR parameters such as the line separation at low temperature and the coalescence temperature T_c are obtained from the temperature variable NMR-spectra. But in all cases (coupled or uncoupled AB case, involving equal or unequal population) total line shape analysis and matching ultimately provides the most reliable method for determing the rate constant corresponding to a particular line shape. However for various practical reasons, there are many instances where one wants a reasonably accurate single rate measurement, usually then converted to a free energy of activation barrier $\Delta G^{\ddagger}$. Of the various simplified procedures, for the uncoupled AB case of equal population, the most widely used is the restricted Gutowsky-Holm coalescence line shape relationship.[27]

$$k_c = \frac{\pi \Delta\nu}{2} \qquad \text{(eq. 8)}$$

$\Delta\nu$ = Line separation without exchange

k_c = rate constant

For the coalescence of the coupled AB case, (eq. 9) is valid.

$$k_c = \frac{(\Delta\nu^2 + 6J^2)^{1/2}}{2} \qquad \text{(eq. 9)}$$

Where J is the coupling constant between nuclei A and B.

The free energy of activation can be calculated from the rate constant (k_r) by means of the Eyring equation.[30]

$$k_r = \frac{k_B \cdot T}{h} \cdot \exp\left(-\Delta G^*/RT\right) \qquad \text{(eq. 10)}$$

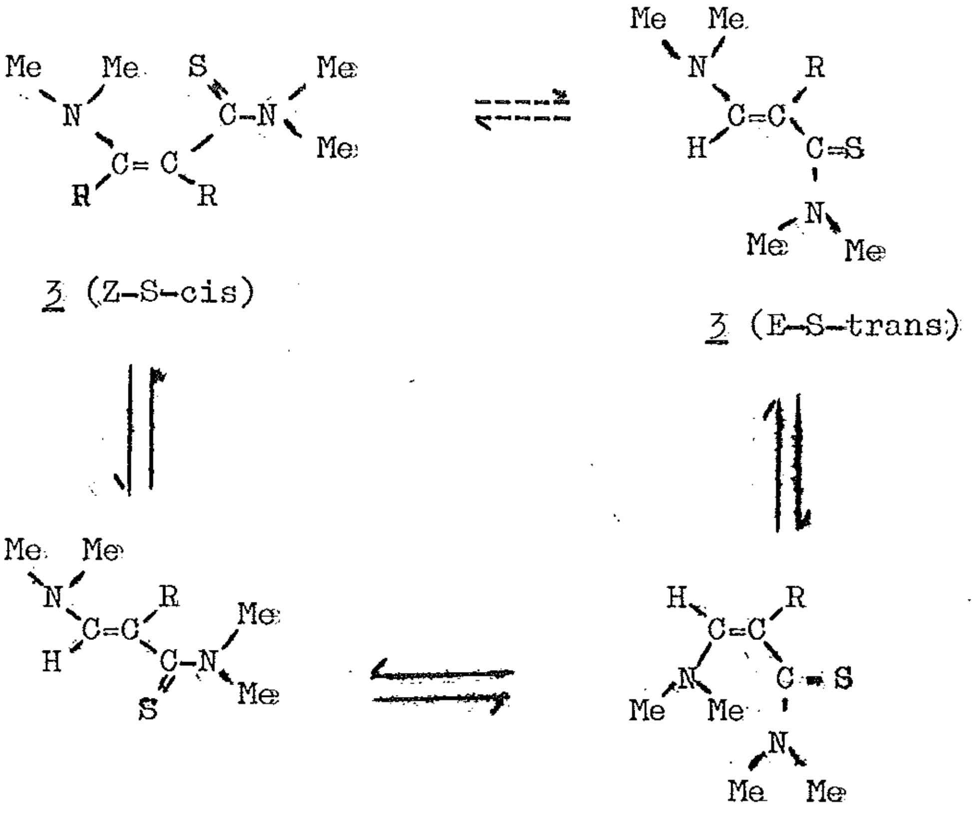
k_B = Boltzman's constant
h = Planck's constant
R = gas constant
T = absolute temperature

$$\Delta G^* = 4.57\, T(10.32 + \log T/k_r) \text{ cal/mole} \qquad \text{(eq. 11)}$$

The free energies of activation ΔG_c^* for the restricted rotations about partial double bonds in the investigated thioacrylamides (see table 3) at the coalescence temperature are readily available from equations 8 and 11 by substituting T_c and $\Delta\nu$ for the corresponding experimentally determined dynamic NMR parameters.

3.2 Lanthanide induced shift method

As mentioned in the introductory part different conformational possibilities exist for the thioacrylamides, e.g. 3. (scheme 2)



3 (Z-S-cis)

3 (E-S-trans)

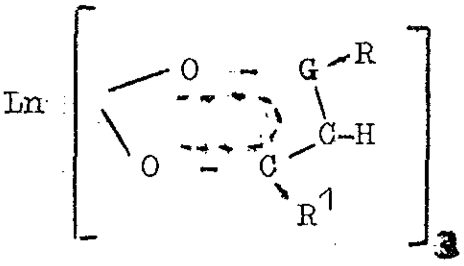
3(E-S-cis)

3 (Z-S-trans)

One way of determining the preferred conformation of such compounds is by using the Lanthanide induced shift method (LIS). Lanthanide shift reagents (LSR) have been extensively applied for the determination of molecular geometry of conformationally rigid compounds. With the aid of LSR's NMR spectroscopy is now being employed to establish the structure and stereochemistry of molecules of such complexity that previously the use of the technique was hampered or altogether preculded both by extensive line overlap and by the complexity of the splitting pattern.

Two methods for the use of LSR's in molecular structure elucidation have evolved. The qualitative approach using chemical shifts and coupling constants derived from shifted spectra (with structural assignments being made on the basis of available emirical knowledge) and the quantitative approach (relying heavily upon the magnitudes and directions of the shifts to confirm or reject proposed three dimensional geometries). The qualitative aspects of the LSR experiments can be sufficient to remove structural ambiguities. The calculation involved in the quantitative procedures are generally computerized with various correlation coefficients being employed to assess the correspondence between computed and observed LIS values.

Property wise Lanthanide shift reagents (LSR's) of the chelate type complexes of paramagnetic rare-earth ions with β-diketones (Fig. 2) are Lewis acids.



tmhd (or dpm)

$R = R' = C(CH_3)_3$

fod: $R = C(CH_3)_3$, $R' = CF_2.CF_2CF_3$

Fig. 2. General structure of Lanthanide shift reagents of the chelate type.

The action of these complexes as shift reagents depends entirely on their ability to form labile adducts with suitable substrates in solution. Lanthanide-induced shifts (LIS's) have been observed with most organic molecules that contain hetroatoms with a lone pair of electrons (Oxygen, nitrogen, sulfur, phosphorus), i.e. substrates possessing some degree of Lewis basicity. The complexed Lanthanide ion expands its co-ordination sphere by interaction with the lone pair of electrons on the donor atom, there by forming a new complex in solution. Under the usual experimental conditions (room temperature, moderate excess of substrate), the equilibrium between substrate molecules co-ordinated to the LIS-complex and excess uncomplexed substrate free in solution is a rapid process on the nmr time scale. Only a time averaged substrate spectrum is, therefore, recorded, and the observed resonance positions of the nuclei are the concentration-weighted averages of the appropriate chemical shifts in the free and complexed substrate. Because of the paramagnetism of the complex, the latter shifts may be very different from the former. The overall effect is that the substrate resonances are shifted from the normal diamagnetic values by an amount which depends on the relative concentration of the shift reagent and the LIS reagent used therefore. More than a mere displacement of spectral lines is involved however. Whereas enhancement of the external magnetic field applied to a sample causes a linear expansion of the spectrum leaving the relative chemical shifts (in ppm) unchanged, the internal secondery field in a paramagnetic system causes a differential expansion of the spectrum, since factors such as the distance of the nuclei from the paramagnetic ion are important. The familiar sequence of signals may, therefore be altered.

Studies with transition metal complexes have revealed that the induced paramagnetic shift may arise by one of two mechanisms. For paramagnetic ions, which possess unpaired electrons, both a Fermi (contact) interaction and a dipolar (pseudo-contact) interaction are possible i.e. unpaired electron spins can perturb the nuclear resonance positions of complexed substrates by a Fermi (contact) interaction, a dipolar interaction or a combination of both mechanisms. Therefore the chemical shift of a given nucleus in the LSR-substrate complex relative to its diamagnetic (uncomplexed) position (Δ_B) can be expressed as the sum of these two contributions. (Eq. 11).

$$\Delta_B = \Delta_{con} + \Delta_{dip}$$ where (eq. 11)

Δ_{con} = the contact shift

Δ_{dip} = the dipolar or pseudo contact shift.

The LIS in resonance of the i^{th} nucleus is given by (eq. 12)

$$\Delta_i^{iso} = \delta_i(S\text{-}R) - \delta_i(S) \qquad \text{(eq. 12)}$$

Δ_i^{iso} = isotopic (paramagnetic) shift.

$\delta_i(S)$ = Chemical shift of free substrate

$\delta_i(S\text{-}R)$ = Chemical shift of complexed substrate

Contact or direct nuclear spin-electron spin interaction requires the presence of a finite unpaired electron spin density at the resonating nucleus. This may occur either from direct delocalization or via spin polarization. Both π and σ bonds may be involved in the process, although the interaction attenuates rapidly through a series of σ-bonds.

Electron-nuclear dipolar interaction is a magnetic field effect acting through space, rather than an effect through bonds, and it gives rise to the so-called pseudo-contact shifts. Thus, in a complex containing several similar nuclei i,j..... the distribution of these shifts can be described solely in terms of the molecular geometry by using the simplified version of McConnel and Robertson's formula[29] (eq. 13).

$$\Delta_{i\,dip} \approx \frac{3\cos^2\theta_i - 1}{r_i^3} \qquad \text{(eq. 13)}$$

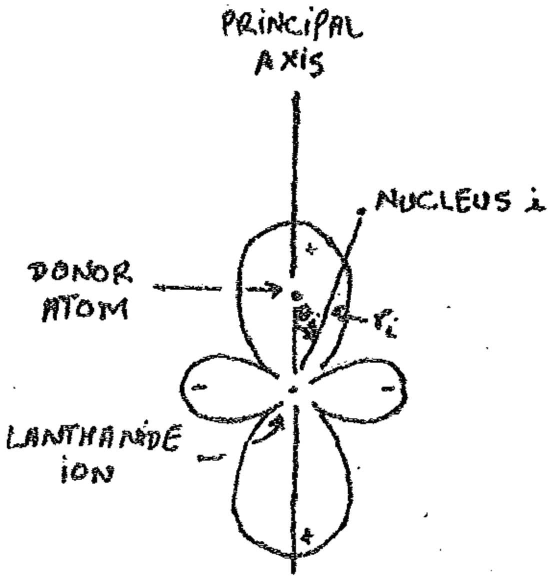


Fig. 3. The dipolar field of an axially symmetric complex

../..

4. Stereochemistry of thioacrylamides

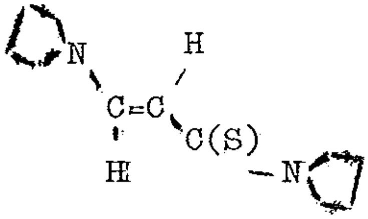
4.1 NMR results

The structues of thioacrylamides 47-53 were established by ^{1}H-NMR analysis. The ^{1}H-NMR results are tabulated below Table 3. Following the table derived conclusions are also given.

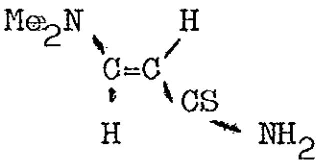
Table 3. ^{1}H-NMR parameters of thioacrylamides 47,48,49,52 and 53

	Chemical shifts( ) in ppm								
Compound	$^{1}CNMe_2$	H^3	$H^2(R^2)$	N-H	$-OCH_3$	Ph	$^{3}(CNMe)_2$	$J_{H_2H_3}(H_Z)$	$J_{NH-H_3}(H_Z)$
47	3.27	8.03	50.20				2.93	11.3	-
48	2.73 and 2.80 2.79 and 2.87	2.22					2.68 2.72	-	-
49	3.52 and 3.18	6.21	7.16				3.01	-	-
52	3.26	7.37	5.32	12.62	3.70	6.62 6.85		9.0	12.0
53	3.23	6.90	7.12	7.52	3.70	6.73		-	12.0

1. The ^{1}HNMR spectral characteristics of compound 43 (Table 3) indicates that the compound might exist in the trans configuration. Both the chemical shift of H^2 and $J_{H_2H_3}$ are in excellent agreement with the values reported for 3-pyrrdidino thioacrylamide[32] 54 and 3-dimethylamino thioacrylamide[33] 55 for which the trans configuration has been assigned.



54



55

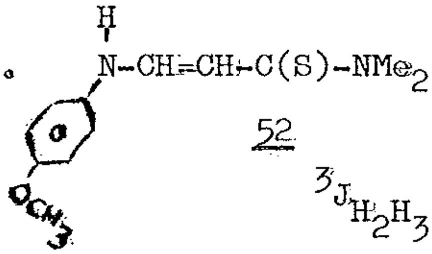
$J^3(H_2H_3$ = 12HZ

(2-H) = 5.14 ppm

$^3J(H_2H_3)$ = 12HZ

δ(2.H) = 5.25 ppm

δ(NMe$_2$) = 2.9 ppm

2. 

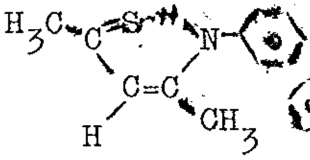
52

$^3J_{H_2H_3}$ = 9.00 HZ

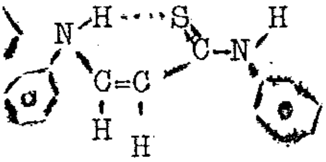
δ(NH) = 12.62

$^3J_{H_3,NH}$ = 12Hz

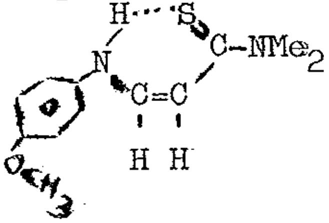
Comparison of the δ(NH) value (12.62 ppm) of 52 with reported δ(NH) values of related compounds 56[22] and 57[32] indicates that this compound has a strong intramolecular hydrogen bond. The $^3J_{H_3,NH}$ (12 HZ) is consistent with the trans arrangement of H_3 and NH groups and the $^3J_{H_2H_3}$(9.00 HZ) is also in the range of cis coupling constants



56

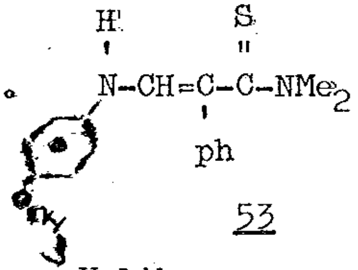


57



52

3.



53

Unlike compound 52, the δ(N-H) value (7.52 ppm) of 53 is shifted to high field but the $^3J_{H_3NH}$ value (12 HZ) indicates that the trans arrangement of H_3 and N-H groups is still preserved. This may be due to the stric effect of the phenyl group which forces the C(1)-N group out of the common plane.

4.2 Dynamic NMR and LIS-study

4.2.1 Determination of rotational barriers

The interaction of the dimethylamino groups of thioacrylamides 47-53 with the thiocarbonyl entity and the consequent double bond character of C-N linkage are determined by both mesomeric and the steric effects. The results of the present dynamic nmr study of the investigated thioacrylamides are in line with these factors.

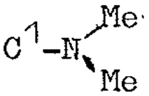
^{1}H-NMR spectroscopy gives at low temperature two lines of equal intensity for the two C(1)-N methyl groups of 47, 49, 52 and 53. We observed the same result for the two C(3)-N methyl groups of 47. The coalescence of these lines at a specific temperature permits the determination of the free energy of activation ($\Delta G_c^{\ddagger}$) for the restricted CN- rotations. Many investigations have shown that the values so obtained are equal to those obtained by line shape analysis, within experimental error. It has also been reported that in this kind of conformational process, $\Delta S^{\ddagger}$ is usually negligible and that $\Delta G_c^{\ddagger}$ can be used as a reliable measure of the barrier independent of the coalescence temperature at which it was determined. The $\Delta G_c^{\ddagger}$ values calculated by using (eq. 11) are tabulated below. (See Table 5).

Compound	T_c (°C)	$\Delta\nu$ (H_Z)	k_c (sec^{-1})	$\Delta G_c^{\ddagger}$ (kJ)mole
$C(1) \circlearrowright N\begin{smallmatrix}Me\\ Me\end{smallmatrix}$				
<u>47</u>	-32	11.7	26	52.1
<u>48</u>	152	-	-	-
<u>49</u>	+120	37.0	82.2	82.6
<u>52</u>	8	16.5	36.7	60.1
<u>53</u>	-6	41.5	92.2	55.1
$C(3) \circlearrowright N\begin{smallmatrix}Me\\ Me\end{smallmatrix}$				
<u>47</u>	-40	26.5	58.9	48.7
<u>48</u>	< -100	-	-	-
<u>49</u>	< -100	-	-	-
<u>50</u>	< -100	-	-	-
$C(1) \circlearrowright N$				
<u>50</u>	100	70	155.5	76.4
<u>51</u>	-42	76	168.8	46.1

Table 5. Coalescence temperatures (T_c), chemical shift differences ($\Delta\nu$), rate constants (k_c) and free energies of activation ($\Delta G_c^{\ddagger}$) of the restricted rotation about partial C,N double bonds in thioacrylamides <u>47</u>-<u>53</u>.

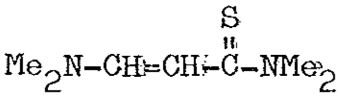
From Table 5, the $\Delta G_c^{\ddagger}$ values (52.1 and 48.7 KJ/mole) for the rotation about C(1)-N and C(3)-N bonds of the unsubstituted thioacrylamide 47 are nearly the same. This barrier value is one evidence for the existence of equal parts of mesomeric interaction of the thiocarbonyl to the vinyl as well as amide nitrogen.


$Me_2N-CH=CH-\overset{S}{\overset{\|}{C}}-NMe_2 \longleftrightarrow Me_2N-CH=CH-\overset{S}{\overset{\|}{C}}-NMe_2$

The low temperature ^{1}H-NMr of 48 and 49 indicates a singlet for the dimethylamino groups of C(3)-N down to -100°C while C(1)-N dimethylamino groups of 49 coalesce at 120° showing a dramatically increased partial fouble bond character to the amide side. This behaviour may be due to the strong steric effect of the phenyl group which forces the  $C^1-N\begin{smallmatrix}Me\\Me\end{smallmatrix}$ entity to be out of the common plane and hence limiting the mesomeric interaction responsible for the restricted rotations to the amide side. This conclusion is further supported by the LIS investigation (see 4.2.2). The existence of the C(3)-N dimethylamino groups of 48 as a singlet upto +150°C and the $\Delta G_c^{\ddagger}$ values of 50 and 51 are additional evidences for this.

4.2.2 Lanthanide induced shift study

The Lanthanide induced shift method was applied for determining the preferred conformations of the investigated thioacrylamides. The spectra were recorded by incremental addition of the LSR Eu(fod)$_3$, to a solution of the compound under study.

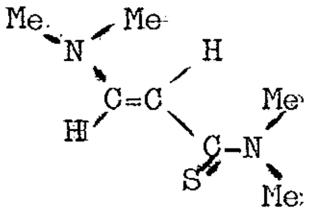
1. 

$Me_2N{-}CH{=}CH{-}\overset{\overset{S}{\|}}{C}{-}NMe_2$

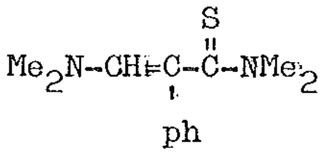
47

From ^{1}H-NMR study (see section 4.1), compound 47 exists in the trans configuration. To determine the preferred conformation from the remaining possible conformers, i.e E-(s-cis) and E-(s-trans), LIS investigation was carried out. The relative paramagnetic shifts (ΔEu) are shown in Fig. 4, i.e $H^3 > H^2 > N^5\!<^{Me}_{Me} > N^4\!<^{Me}_{Me}$

Based on the distance dependence of observed relative paramagnetic shifts ΔEu($\propto r^{-3}$) in the MeConnel Robertson formula (eq. 13), ^{1}H NMR study $[^3J_{H_2H_3}]$ and also by using a model, we assigned the E-(s-cis) conformation to compound 47.



E-(s-cis)

2. 

$Me_2N{-}CH{=}\underset{\displaystyle ph}{C}{-}\overset{\displaystyle S}{\overset{\|}{C}}{-}NMe_2$

49

Basic strength and steric hinderance are the factors primarily responsible for the degree of binding between shift reagent and substrate. Consequently, the magnitude of the induced paramagnetic shift ΔEu depends markedly on these two factors.

The spectrum of compound 49 (fig. 4) shows no change in the isotropic shifts even at a very high concentration of Eu(fod)$_3$. This may be due to the absence of any coordination between the shift reagent and substrate. This result coupled with the dynamic behavior of the dimethylamino groups of 49 confirms once more the strong steric effect of the phenyl group.

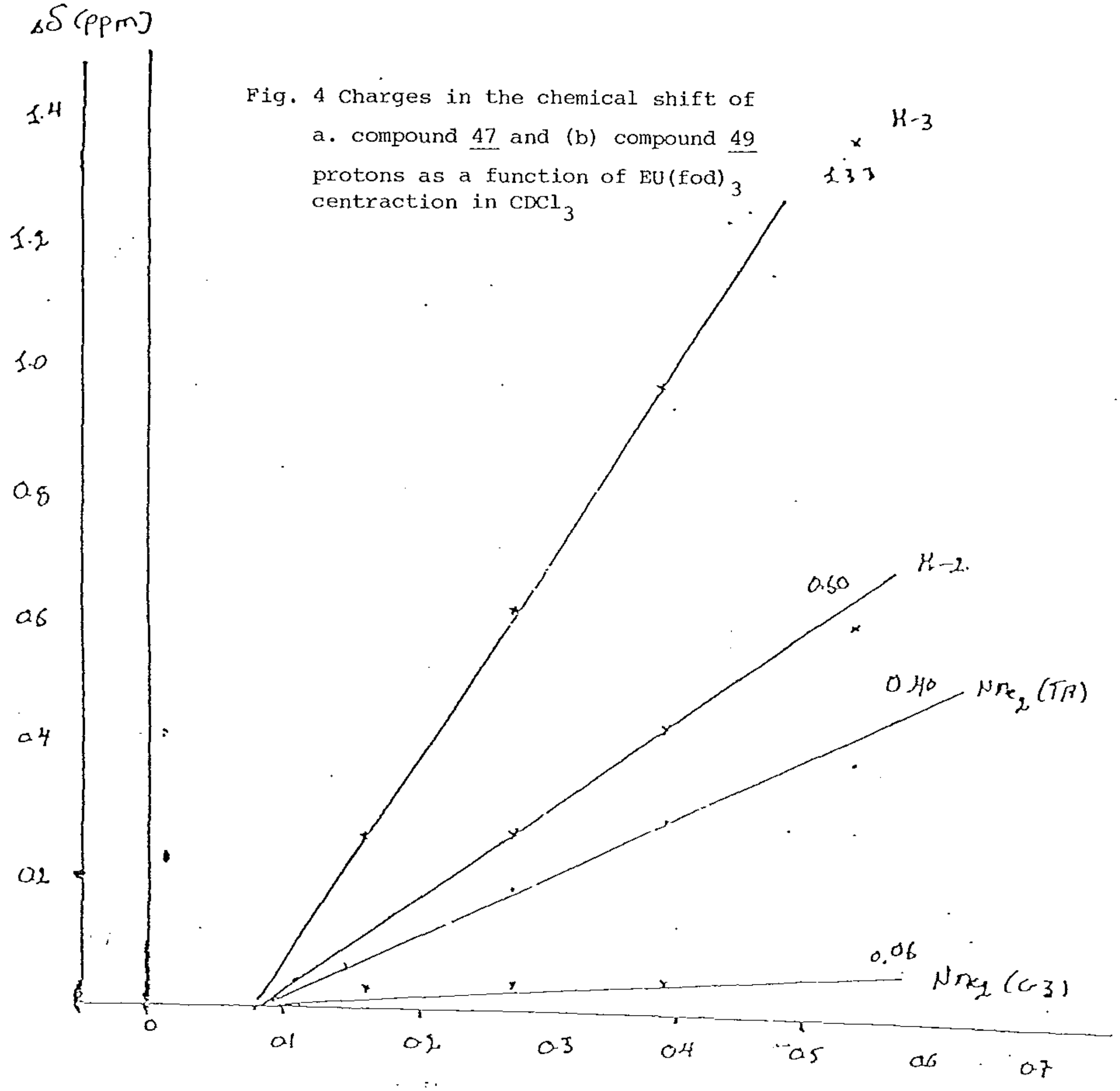
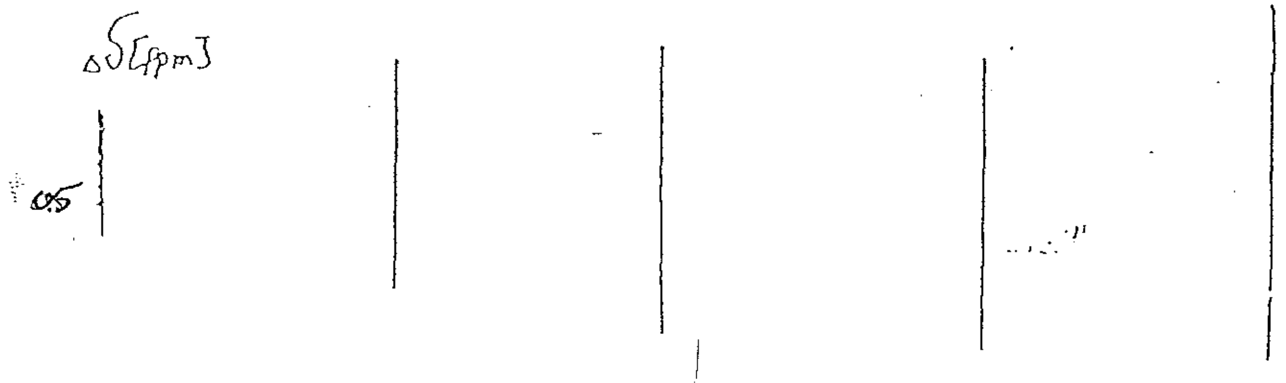


Fig. 4 Charges in the chemical shift of a. compound <u>47</u> and (b) compound <u>49</u> protons as a function of EU(fod)$_3$ centraction in CDCl$_3$



5. Experimental

^{1}H-NMR spectra were recorded at 60 MH_z on a Varian A-60 spectrometer. TMS was used as internal standard and chemical shifts are expressed in δ-values. $CDCl_3$ was used as the solvent.

Dynamic NMR spectra were recorded by TESLA Bs 487 C spectrometer with standard variable temperature probe and temperature controller.

The shift investigation was carried out by Varian A-60 spectrometer using $Eu(fod)_3$ as LIS reagent. $CDCl_3$ was used as the solvent.

IR spectra were recorded by Perkin-Elmer, Model 727 - B spectrometer. Values are given in cm^{-1}.

Melting point (m.p) was determined by uni-melt. Thomas Hover capillary melting point apparatus and are uncorrected.

5.1 Synthesis of N,N-Dimethylamides

A. N,N-Dimethylphenyl acetamide 7

A mixture of 15.7 g of phenylacetylchloride and 15 g of N,N-Dimethyl formamide was heated together at 150° for four hours. The product was distilled under reduced pressure and yielded 15.2 g of N,N-Dimethylphenyl acetamide. M.pt. 42-43°C yield 97% Lit. m.pt. 42-43°C.

^{1}HNMR: 2.7 (singlet/6 protons), 3.5 (singlet/2 protons), 7.00 (singlet/5 protons).

N,N-Dimethylpropionamide 4

A mixture of propionic anhydride, 26.4 g, N,N-Dimethyl formamide 25 g, and one drop of concentrated sulfuric acid was heated under reflux for six hours. The mixture was then distilled. The amount of N,N-Dimethylpropionamide was 26.45 g yield 90.5%. B.pt. 166°C/585 MM_{Hg}. Lit. b.pt 176°/76. MM_{Hg}.

^{1}H-NMR: 1.2 (triplet/3 protons), 2.4 (quartet/2 protons), 3.00 (doublet/6 protons).

Compound	M.pt(°C)	B.pt(°C)	Lit.b.pt	Yield(%)	IR/thinfilm $\overset{O}{\parallel}$ $-C-NMe_2/cm^{-1}$	^{1}H-NMR
4	-	166/585	176/765	90.5	1650	See B
+5	-	125/100	125/100	89.5	1645	0.79 (triplet/3 protons) 1.45 (multiplet/2 protons) 2.1 (triplet/2 protons) 2.81 (doublet/6 protons)
+6		141/100	125/100	90.9	1650	1.2 (triplet/3 protons) 2.42 (quarter/2 protons) 2.98 (doublet/6 protons)
7	42-43			91		See A

+Prepared in a similar way as compound 7.

5.2 N,N-Dimethlthioamides

A. N,N-Dimethylphenyl-thioacetamide 13

A mixture of N,N-Dimethylphenyl-acetamide 7 (6.52 g), Lawesson's reagent 8 (9.84 g) and dry toluene (5 ml) was heated to 100°C for four hours in a 100 ml three necked flask equipped with magnetic stirrer and calcium chloride tube. The mixture was allowed to cool to room temperature. The toluene was removed by distillation and the residue was purified on a silica gel column with Ethylacetate/petroleum ether (10:90). Yield 69% M.pt. 78-80°C. Lit. m.pt. 79-80°C.

^{1}H-NMR: 3.08 (singlet/3 protons), 3.37(singlet/3 protons)
4.23 (singlet/2 protons), 7.30 (singlet/5 protons)

B. N,N-Dimethylthioacetamide 9

A mixture of N,N-Dimethylacetamide (20 g) and 100 ml redistilled xylene was taken in a 500 ml three necked flask. P_2S_5 was added to the mixture by stirring at toom temperature. Then 29 g of Na_2S was added portionwise and the mixture heated for one hour to 70-80°C. After extracting the reaction product with xylene several times at 80°C, the solution was concentrated and precipitated by adding petroleum ether. M.pt. 73-75°C. Yield 63.35%

^{1}HNMR: 2.64 (singlet/3 protons), 3.4 (doublet/6 protons)

IR/kBr, N-C=S/cm^{-1} = 1326

C. Phenylthioacetomorpholide, 14

Acetophenone (12 g), morpholine (8.7 g) and sulfur (3.2 g) were mixed and refluxed for eight hours, and the mixture poured into 50 ml of hot ethyl alcohol. The crystalls of phenylthioacetomorpholide which formed om cooling melted at 77-79.5°C. Lit. m.pt. 78-79.5°C.

Yield: 72%

^{1}H-NMR: 3.58 (multiplet/6 protons), 4.23 and 4.26 (triplet/2 protons).
4.25 (singlet/2 protons), 7.23 (multiplet/5 protons).

Table 7. Data table for N,N-Dimethylthioamides

Compound	M.pt.(°C)	%yield	^{1}H-NMR
9	73-75	75	See B
[a]10[+]			1.19 (triplet/3 protons, 2.62(quartet/2 protons), 3.22(doublet/6 protons)
[a]11[+]			1.2(triplet/3 protons), 1.8 (multiplet/2 protons), 2,8 (triplet/2 protons), 3.4 (doublet/6 protons).
[a]12[+]			1.2 (doublet/6 protons), 2.4 (heptate/1 proton), 2.85 (doublet/2 protons), 3.6 (doublet/6 protons)
13	78-80		See A
14	77-79.5	72	See C

[+] Prepared in a similar way as compound 13.

[a] Very low yields.

5.3 Synthesis of thioacrylamides

A. 3-Dimethylamino-N,N-dimethylthioacrylamide, 47

A mixture of N,N-Dimethylthioacetamide (3.1 g), Bis-(dimethylamino)-tert-butoxymethane (5.22 g) was taken in a 50 ml three necked flask equipped with a stirrer and a reflux condenser. The mixture was heated for one hour on a water bath. After distilling out tert-butanol and dimethylamine from the reaction mixture, the crude product was purified by dissolving in $CHCl_3$ and precipitating with cyclohexane. M.pt. 123-124°C. Lit. m.pt = 124°C. Yield 63%

^{1}H-NMR (see Table 3).

B. 3-Anisidino-N,N-dimethylthioacrylamide, 52

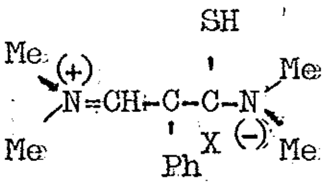
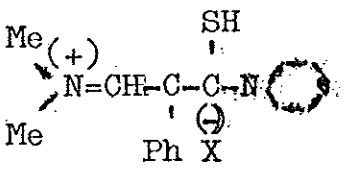
A mixture of 47, (1.58 g), 15 ml ethanol and p-methoxyaniline (2 g) was heated to boiling for about 30 minutes. The reaction product was allowed to cool to room temperature. The precipitated anisidino compound was then suction filtered. Yield 73.2% M.pt. 118-120°C. ^{1}H-NMR (see Table 3).

C. 3-Mercapto-2-propeniminium salts

Phosphoryl chloride (1.54 g, 0.01 mole) was added dropwise to a stirred cooled solution of N,N-Dimethylformamide (0.01 mole) in CCl_4 (5 ml). Then the substituted thioacetamide (0.01 mole) was added and the mixture was heated to gentle boiling for 30 min.

The warm mixture was then mixed with an equal amount of glacial acetic acid to which was added about 15 ml of perchloric acid. The iminimum salt was precipitated as the perchlorate by the addition of ether, isolated by suction and washed with glacial acetic acid. Following this general procedure, the iminium salts were synthesized (see Table 8).

Table 8. Data table for 3-mercapto-2-propeniminium salts

Compound	Structure	M.p(°C)	Lit.m.pt	Yield %
<u>45</u>		180-182	-	52
<u>46</u>		140-141	140-141	71

$\overset{(-)}{X} = ClO_4^{(-)}$

D. 3-Dimethylaminopropenthioamides

Triethylamine (1,2 g, 0.012) was added to the solution of the appropriate 3-mercapto-2-propeniminium perchlorate (0.01 mole) in acetonitrile (10 ml). The mixture was then diluted with water and left for some days. The precipitated product was then isolated by suction.

Table 9. Datattable for 3-dimethylaminopropenthioamides

Compound	M.P(^{o}C)	Lit.m.pt	Yield%	^{1}H-NMR
<u>49</u>	76-79	-	71	See Table 3
<u>50</u>	107-108	107-108	74	2,75 (doublet/6 protons) 3.75 (multiplet 6.00 (singlet/1 proton) 7.00 (singlet/5 protons)

E. 3-Hydroxypropenthiomorpholide

A mixture of 3-Dimethylaminopropenthiomorpholide (2.76 g), glacial acetic acid (7 ml), and water (7 ml) was heated to boiling for 5 minutes and the solution then diluted with water (50 ml). After the resulting oily product has solidified it was isolated by suction and dried. Yield 79% M.pt. 129-130^{o}C. Lit.m.pt = 129-130^{o}C

^{1}H-NMR: 3.5 (triplet.4 protons), 2.73 (triplet/4 protons), 7(singlet/1 proton), 7.2(doublet/5 protons).

IR/KBr, OH/cm^{-1} = 3110

F. 3-Anisidino-N,N-Dimethyl-2-phenylthioacrylamide, 53

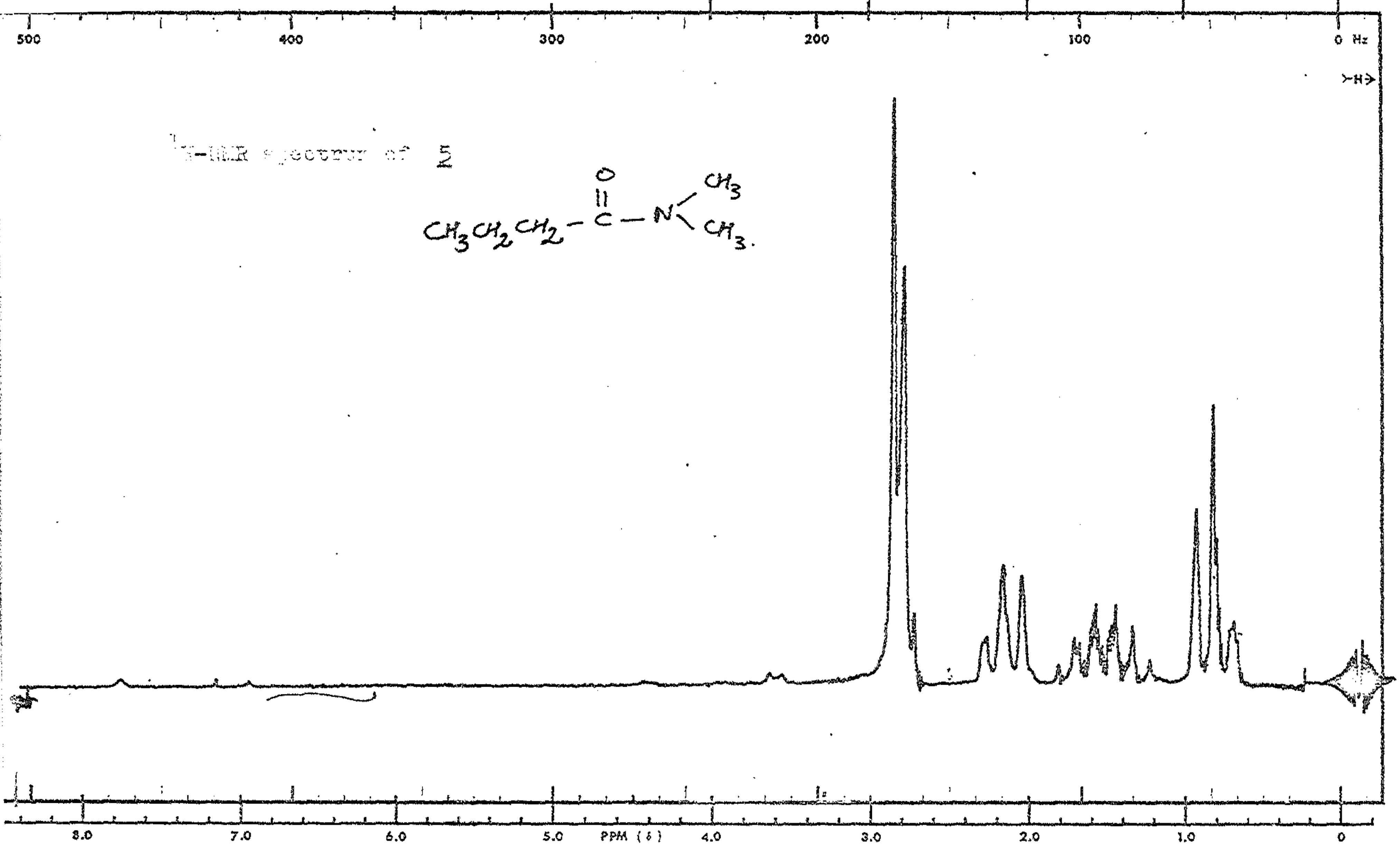
A mixture of 45 (3.34 g), 15ml ethanol and p-methoxy-aniline (2 g) was heated to boiling for about 15 minutes. The reaction product was allowed to cool to room temperature. The precipitated anisidino compound was then suction filtered. Yield 82% M.p. 137-139°C

NMR: See Table 3.

Table 10. Data table for thioacrylamides 47-53

Compound$^+$	M.P(°C)	%Yield
47	123-124	63
48$^+$		
49	76-79	71
50	107-108	74
51	129-130	79
52	118-120	73.2
53	137-139	82

$^+$Prepared in the same way as compound 47



¹H-NMR spectrum of 5

$CH_3CH_2CH_2-\overset{O}{\overset{\|}{C}}-N\begin{smallmatrix}CH_3\\CH_3\end{smallmatrix}$

MANUAL

EEP OFFSET (Hz): -------
ETRUM AMPLITUDE: -------
EGRAL AMPLITUDE: -------
NNING RATE (RPS): -------

SWEEP TIME (SEC): 50 250
SWEEP WIDTH (Hz): 25 50 100 250 500
FILTER: 1 2 3 4 5 6 7 8
RF POWER LEVEL: ------------

AUTO ☐
(250)
(500)
(2)
(.05)

SAMPLE: $CH_3-CH_2-CH_2-C\overset{O}{=}-N\begin{smallmatrix}Me\\Me\end{smallmatrix}$

REMARKS:

SOLVENT: $CDCl_3$ / TMS

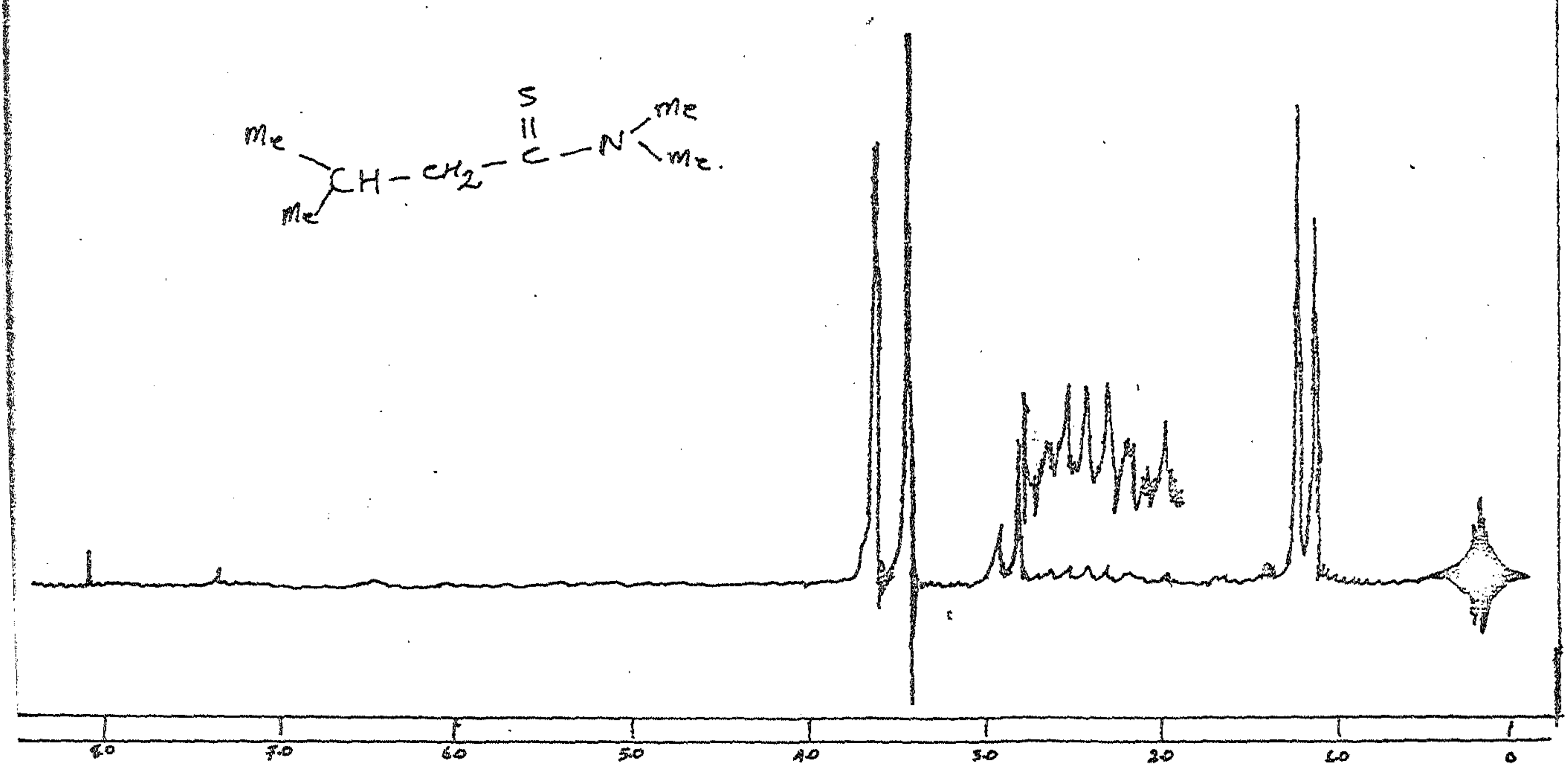
varian
analytical instrument division

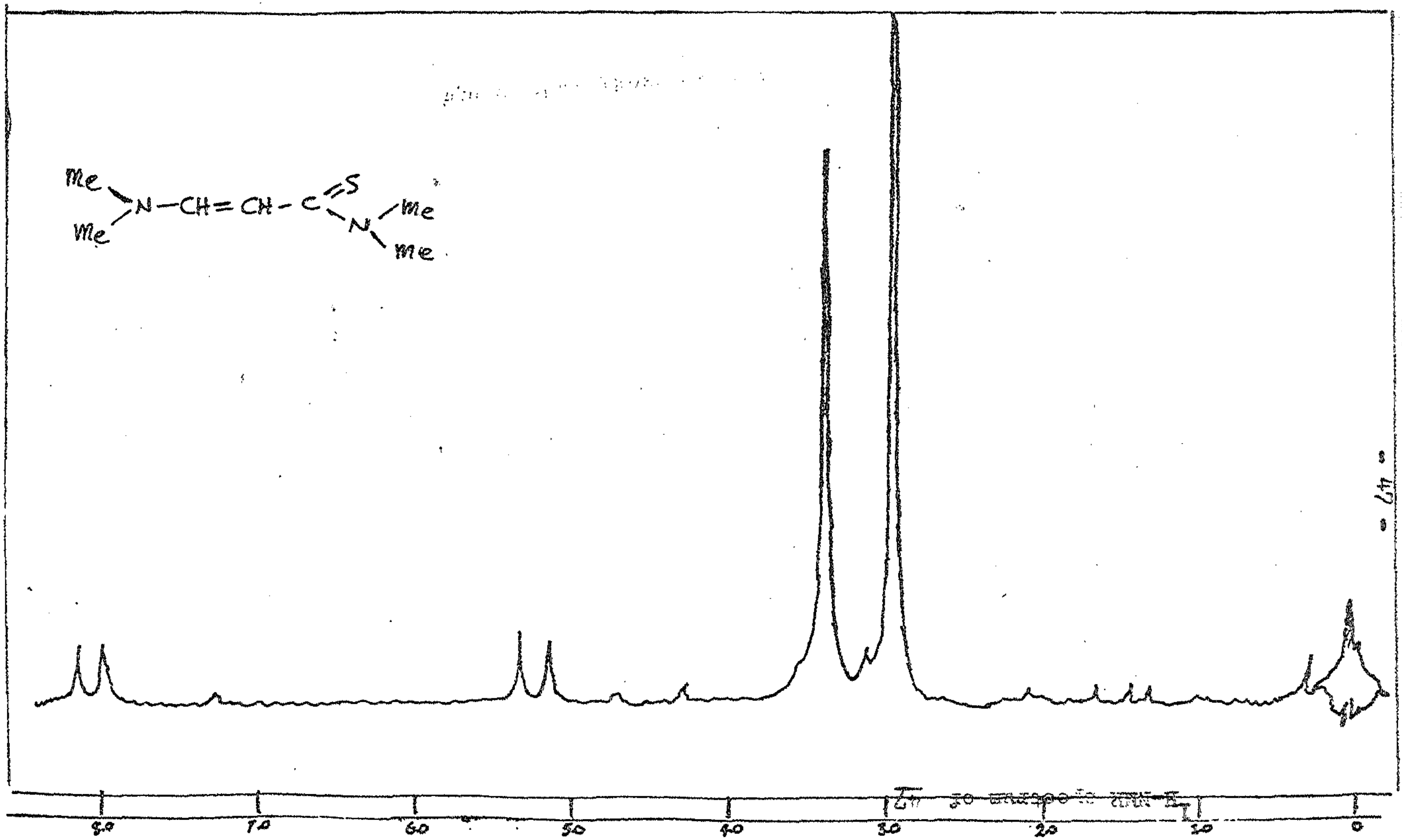
DATE: 11 10/83

OPERATOR:

60 MHz NMR

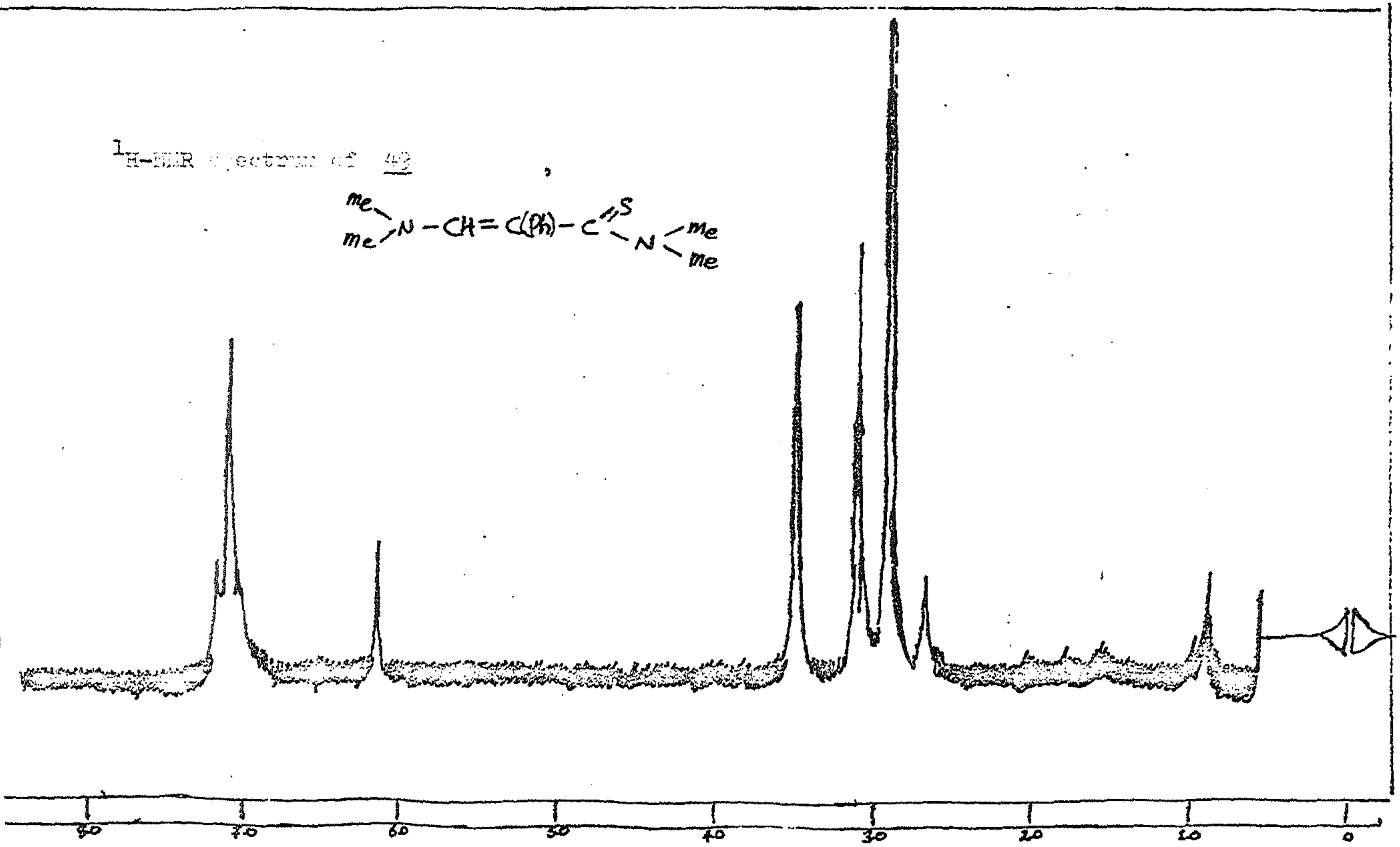
¹H-NMR spectrum of 12





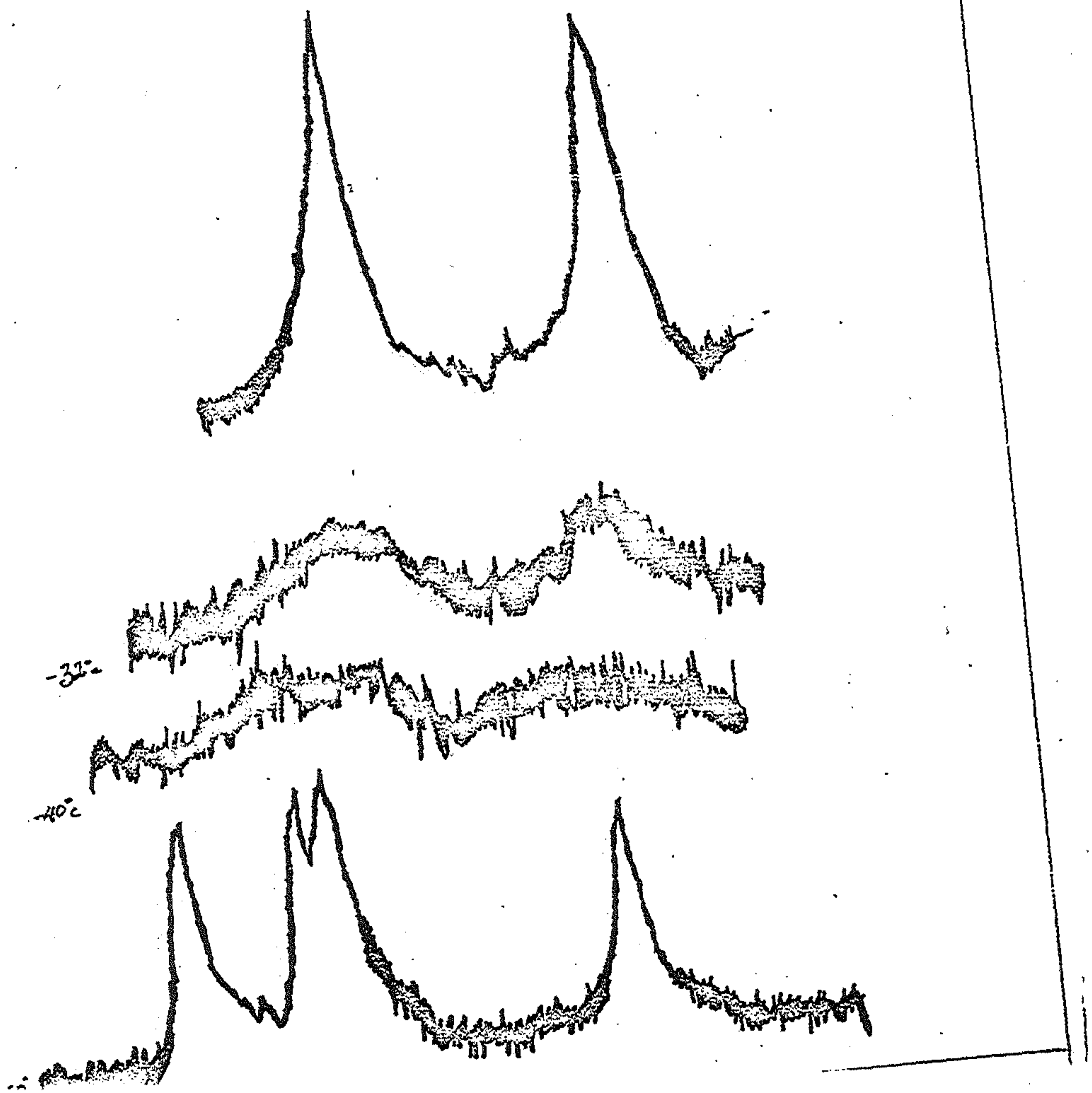
^{1}H NMR spectrum of **47**

^{1}H-NMR spectrum of 42



$$\mathrm{me_2N{-}CH{=}C(Ph){-}C({=}S){-}N(me)_2}$$

[illegible] #7



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